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10/561,005

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EXAMINER

MARVICH, MARIA

ART UNIT

PAPER NUMBER

1633

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/561,005	Applicant(s) EINAT ET AL.	
	Examiner MARIA B. MARVICH	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 and 28 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-20 and 28 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 December 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/15/05, 5/30/06</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claims 1-20 and 28 are pending in this office action. .

Information Disclosure Statement

IDS' filed 12/15/05 and 5/30/06 have been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action. The documents listed as International Search Reports, Written Opinions are not considered to be a document under 37 CFR 1.98. Therefore, references have been considered but have been crossed off the 1449 so that it will not appear on the face of any patent issuing from the instant application.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, the letter stating that the contents of the sequence listing and the CRF are the same is missing. A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, CRF and letter stating that the contents of the sequence listing and the CRF are the same and contain no new matter is required. .

Specification

The specification is objected to for minor informalities. The brief description of drawings is objected to because Figure 4 contains an A, B and C portion. However, the description does not describe each portion.

Claim Objections

Claims 1, 2, 6, 7, 10 are objected to because of the following informalities: claims 1 and 10 recite, "A process of cloning a nucleic acid in a desired orientation".

Recommendation is made to amend the claims to further conform with the limitations and steps recited to, --A process of cloning a double-stranded nucleic acid into a vector in a desired orientation--. Thereafter the article "the" can be used to reference these limitations as "a" refers to a newly recited limitation. Finally, the step d) recites "cloning the double-stranded nucleic acid into a desired vector". As the claims include a non-amplified and an amplified double stranded nucleic acid, it would be remedial to indicate which is which. In step d) it would be remedial to amend the claim to recite, --cloning the amplified double-stranded nucleic acid into the vector--.

Claims 2 and 14 recite that the nucleic acid "is genomic DNA". As the claim as recited suggests that the nucleic acid is the whole of the genomic DNA, it would be clearer to recite, --the double stranded nucleic acid is from genomic DNA--.

Claim 6 recites "using a primer complementary to the primer of claim 5. It appears as if this complementary primer is "used" to amplify the single stranded nucleic

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acid or else a double stranded nucleic acid following amplification from the 3' end.

However, the claim does not set forth the use required of the claim.

Claim 7 recites "the primer" in claim 5. To more clearly distinguish between primers it would be clearer to refer to for example, the 3' ligated primer, the 3' complementary primer, the 5' ligated primer, the 5' complementary primer.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: what part of the method leads to cloning in a "desired orientation". The instant claims are drawn to a method of cloning double stranded nucleic acid fragments into vectors in desired orientation. The method simply involves ligation of a primer to the 3' end of a single stranded nucleic acid, amplification of the nucleic acid followed by its cloning into a vector. The method lacks any steps that indicate how cloning in a desired orientation is affected by the steps. The specification teaches that cloning in a desired orientation cannot occur unless the

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nucleic acid has a recognizable region such as a poly-A region or a CAP region.

Secondly, expression of cDNA can be problematic if proceeding from the antisense strand. The instant invention initiates the method with a single-stranded nucleic acid, which comprises 5' phosphates on one terminus and 3' hydroxyl groups in the other. Thus, primers will ligate to the 3' end "Ligation of an adaptor or oligonucleotide to the 3' terminus of the single stranded nucleic acid fragment (such as ssDNA or ssRNA) is accomplished by modifying the oligonucleotide in such a way that it will ligate only to an OH (i.e., hydroxyl) tail. For this purpose, an oligonucleotide should have a phosphate on its 5' terminus and should be blocked on its 3' terminus. This blocking is necessary to ensure that the oligonucleotide will not ligate to the 5' terminus of the single stranded nucleic acid." As well, the disclosure further comprises annealing a primer with a restriction site to the 5' end of the double stranded nucleic acid, digesting with the enzymes and inserting the digested ends into a cloning vector. However, the claims do not utilize the restriction recognition sites as currently recited. As these are two methods of driving cloning in the proper orientation but the claims lack either, the claims lack critical elements that lead to cloning in a desired orientation.

The term "specific" in claim 5 is a relative term which renders the claim indefinite. The term "specific" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear to what the primer is specific.

Claim 18 refers to a step of digesting the fragment of step (a) into smaller fragments. However, it is not clear when this step is to be performed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10, 11, 13, 16 and 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Simonestis et al (5,183,748; see entire document).

Simonestis teach the addition of adaptors to single stranded oligoribonucleotides by T4 DNA ligase to the 3' end and 5' end (see e.g. figure 10). The adaptors differ in the restriction sites that they encode. The resulting DNA is amplified with Klenow (see e.g. col 4, line 24-35). Then the amplified fragment is inserted into a vector see figure 12 in a desired orientation. The primers can have a 3' or a 5' overhang as recited in claim 11 (see e.g. figure 6).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 10-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simonestis et al (5,183,748; see entire document) in view of Zhang et al (NAR, 1996,

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Vol 24 (5), pages 990-991; see entire document) and Broude et al (US 2004/0126760; see entire document).

Applicants claim a method of cloning in which double stranded adaptors are ligated to single stranded genomic DNA or cDNA..

The teachings of Simonestis are as above except;

Simonestis et al do not teach use of genomic or cDNA as a template for ligation of the primers.

Zhang et al teach the ligation of single stranded primers by T4 RNA ligase to the 3' end of genomic or cDNA single stranded DNA (see e.g. figure 1). Furthermore, a 5' primer was added to the DNA. Primers complementary to the primers were used to amplify the DNA (see e.g. figure 1 and page 991, col 2, paragraph 1).

Broude teaches preparation of adapters for ligation to nucleic acid such as single-stranded nucleic acid. The adapters are 5'overhand adapters (see e.g. ¶ 0037). The adapters include restriction sites (see e.g. ¶ 0035).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the oligoribonucleotides taught by Simonestis with the genomic or cDNA taught by Zhang et al and the adapters taught by Broude et al because Simonestis et al teach that it is within the ordinary skill of the art to ligate double stranded adaptors to single stranded oligoribonucleotides and because Zhang et al teach that it is within the ordinary skill of the art to ligate primers to single stranded genomic or cDNA. One would have been motivated to do so in order to receive the expected benefit of increased targets for cloning and inserted adapters with restriction sites. Based upon the teachings of the cited references, the high skill of one of ordinary

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skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention. Furthermore, in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that substitution of genomic DNA or cDNA for ribonucleotidies or one adapter for another is done applying a known method with predictable results.

Claims 1-9, 20 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (NAR, 1996, Vol 24 (5), pages 990-991; see entire document) in view of Shuman (US 6,548,277 B1; see entire document) and further in view of Hite et al (NAR, 1996, Vol. 24 (12), pages 2429-2434

Applicants claim a method of cloning in which single stranded DNA is ligated with an oligo primer encoding at least one restriction enzyme site at the 3' and 5' ends. The DNA is amplified by Klenow.

Zhang et al teach the ligation of single stranded primers by T4 RNA ligase to the 3' end of genomic or cDNA single stranded DNA (see e.g. figure 1). Furthermore, a 5' primer was added to the DNA. Primers complementary to the primers were used to amplify the DNA (see e.g. figure 1 and page 991, col 2, paragraph 1).

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Zhang et al do not teach that the primers encode restriction recognition sites.

Neither does Zhang et al teach the use of Klenow to amplify the DNA.

Shuman teaches that it is commonplace to introduce a restriction site into the PCR primer and to cleave the PCR products with that restriction enzyme to facilitate joining by ligase to vector (see e.g. bridging paragraph 7-8).

Hite et al teach use of Klenow, which greatly reduced the occurrence of frameshift products (see e.g. abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute primers and DNA polymerase taught by Zhang et al with the primers comprising restriction endonuclease recognition sites taught by Shuman and the Klenow taught by Hite et al because Zhang et al teach that it is within the ordinary skill of the art to ligate single stranded primers to single stranded DNA and because Shuman teaches that it is within the ordinary skill of the art to include restriction sites in the primers and because Hite et al teach that it is within the ordinary skill of the art to use Klenow for amplification. One would have been motivated to do so in order to receive the expected benefit of increased fidelity of Klenow and of generating DNA fragments with restriction sites for ease of cloning. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
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